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(54) Title: COMBINATION THERAPY FOR TREATMENT OF SCHIZOPHRENIA

(57) Abstract: The present invention is directed to a new treatment for schizophrenia. It has been discovered that schizophrenia will respond to the combination of an atypical antipsychotic and a valproate compound. This combination is especially useful for alleviating the acute symptoms of schizophrenia. The invention also extends to new formulations containing an antipsychotic in combination with a valproate compound.

COMBINATION THERAPY FOR TREATMENT OF SCHIZOPHRENIA

The present invention is directed to the use of a valproate compound and an atypical antipsychotic in the treatment of schizophrenia. Other aspects of the invention are directed to pharmaceutical compositions containing both a valproate compound and an atypical antipsychotic.

Background

Psychotic conditions such as schizophrenia and related disorders (e.g. schizoaffective disorder) are complex and heterogeneous diseases of uncertain etiology that afflict approximately 1 to 2% of all populations worldwide. Schizophrenia is characterized as having both "positive symptoms" (hallucinations, delusions, and conceptual disorganization) and "negative symptoms" (apathy, social withdrawal, affect, and poverty of speech). Abnormal activity of the neurotransmitter dopamine is a hallmark of schizophrenia. Dopaminergic activity is reduced in the mesocortical system (resulting in negative symptoms) and is enhanced in the mesolimbic system (resulting in positive or psychotic symptoms).

Since the most overt signs of schizophrenia are associated with excess dopaminergic activity, initial drug therapy focused on blocking dopamine receptors in the CNS. Chlorpromazine was the first such agent to be developed for schizophrenia, dating to the 1950's. Chlorpromazine has high affinity for the D_2 receptor, functioning as an antagonist at that receptor.

A number of other D_2 antagonists were subsequently developed. These D_2 antagonists are often referred to as "neuroleptics" or "classical antipsychotics". Examples of such D_2 antagonists include thioridazine, fluphenazine, haloperidol, thioxanthene, flupenthixol, molindone, and loxapine. These D_2 antagonists are effective for treating the positive symptoms of schizophrenia, but have little or no effect on the negative symptoms. A further disadvantage of D_2 antagonists is the high incidence of extrapyramidal side effects, including rigidity, tremor, bradykinesia (slow movement), and bradyphrenia (slow thought), as well as tardive dyskinesias and dystonias.

Due to the significant side effects and limited efficacy associated with D_2 antagonists, researchers attempted to find new antipsychotic agents having differing mechanisms of action. Researchers looked at other neurotransmitters within the CNS to determine what impact, if any, they might have on schizophrenia. Neurotransmitters that have been studied included serotonin ("5HT"), and gamma-aminobutyric acid("GABA"). Researchers have also

evaluated the ability of phospholipase inhibitors, neurokinin antagonists, AMPA modulators, and opioid antagonists to alleviate schizophrenia.

These efforts led to the development of a new class of antipsychotics that alleviate schizophrenia by mediating serotonergic transmission within the CNS. These agents are commonly referred to as the "atypical antipsychotics". All of the atypical antipsychotics bind to $5HT_2$ receptors within the CNS. These compounds act as antagonists of serotonin at these $5HT_2$ receptors. A detailed discussion of the mechanism of action of the atypical antipsychotics is described by Lieberman et al, Biol. Psychiatry 1998:44:1099-1177. Examples of such agents include clozapine, olanzapine, and risperidone.

At least two distinct GABA receptors have been identified to date, $GABA_A$ and $GABA_B$. Wassef et al. J Clin Psycholpharmacol 1999;19:222-232. Researchers postulated that $GABA_B$ agonists would have utility in schizophrenia, since these agonists down regulate dopaminergic transmission within the CNS. Examples of such GABA agonists include the benzodiazepines (i.e. valium, librium, etc.), vinyl GABA, and valproic acid. Despite the theoretical promise, clinical studies with these $GABA_B$ agonists have produced mixed results, Wassef supra.

Researchers have also attempted to treat schizophrenia by using combinations of drugs having differing mechanisms of action. Wassef et al reported on the use of a D_2 antagonist (haloperidol) in combination with a $GABA_B$ agonist (divalproex sodium) to alleviate acute exacerbations of schizophrenia J. Clin Psychopharmacol Vol 20 No. 3 357-361 (2000). Wassef et al evaluated this combination in a clinical trial involving 12 patients. The treatment group received haloperidol and divalproex sodium. The control group received haloperidol alone. The treatment group showed greater improvement than the control group. The authors concluded that such combinations merit further study.

Kausen et al reported on a study involving 14 chronic schizophrenics who had been maintained on clozapine (an atypical antipsychotic) for at least 2 years (Neuropsychobiology 11:59-64 (1984). Sodium valproate was instituted in these patients for 90 days and then discontinued. The patients' symptoms were evaluated while receiving the combination and with clozapine alone. Valproate did not have any significant effect on the patients symptoms.

While clozapine has shown significant efficacy in controlling the negative symptoms of schizophrenia, its widespread use has also highlighted some serious side effects. One of the more serious side effects is seizures. Balen reported on using valproate prophylactically to prevent seizures in patients taking clozapine (Int. J. Psychiatry Clin. Pract. ¾ (249-251) (1999) No impact on the symptoms schizophrenia was described. Taner et al also described similar results Int. J. Psychiatry Clin Pract. 2/1(53-55) (1998).

In view of the wide spread incidence of schizophrenia and the significant economic costs associated with this disease, new treatment regimens still remain a valuable contribution to the art.

SUMMARY OF THE INVENTION

In accordance with the present invention, a new therapeutic regimen for the treatment of schizophrenia has been discovered. It has been discovered that schizophrenia can be treated by concurrently administering to a patient with schizophrenia an atypical antipsychotic and a valproate compound.

In a further embodiment, it has been discovered that this combination is especially beneficial for treating schizophrenics during the acute phase of their disease. The acute phase is characterized as a florid psychotic phase. It may include violent or dangerous behaviors, hallucinations, delusions, hostility, bizarre behavior, paranoia, etc. During this acute phase, it is almost impossible for patients to function in normal social settings. Patients are typically hospitalized during this acute phase. This acute phase is also typically referred to as psychosis associated with schizophrenia.

The addition of a valproate compound will enhance the patients' recovery from this acute phase of schizophrenia. The symptoms of psychosis will subside at a quicker rate, than in a patient who is taking only an atypical antipsychotic. Thus, the valproate will serve to shorten the period of time that the patient is exhibiting these overt symptoms of psychosis and potentially shorten the duration of their hospitalization.

The combination of a valproate compound and an atypical antipsychotic is also useful in the treatment of other mental illnesses, besides schizophrenia. Psychosis is often associated with schizophreniform and dementia. The psychosis associated with these diseases will resolve at a quicker rate when the patient is treated with the combination of this invention.

DETAILED DESCRIPTION OF THE INVENTION

A) Schizophrenia

Schizophrenia, a major psychotic disorder, is a chronic condition that frequently has devastating effects on a patient's life and carries a high risk of suicide and other life-threatening behaviors. Manifestations of the disorder involve multiple psychological processes, including perception (e.g., hallucinations), ideation, reality testing (e.g." delusions), emotion (e.g., flatness, inappropriate affect), thought processes (e.g., loose associations), and behavior (e.g., catatonia, disorganization). The behavioral and psychological

characteristics of schizophrenia are associated with a variety of impairments in social and occupational functioning.

The principal manifestations of schizophrenia are described in terms of positive and negative (deficit) symptoms and, disorganized symptoms, Positive symptoms include hallucinations, delusions, bizarre behavior, hostility, uncooperativeness, and paranoid ideation. Negative symptoms include restricted range and intensity of emotional expression (affective flattening), reduced thought and speech productivity (alogia), anhedonia, apathy, and decreased initiation of goal-directed behavior (avolition). Disorganized symptoms include disorganized speech (thought disorder) and behavior and poor attention. Subtypes of schizophrenia include the paranoid, disorganized, catatonic, undifferentiated, and residual types. Management of schizophrenia usually involves a variety of interventions (e.g., psychiatric management, psychosocial interventions, drug therapy, electroconvulsive therapy, etc.) aimed at reducing the frequency, severity, and psychosocial consequences of acute episodes and at reducing the overall morbidity and mortality of the disorder. Most patients alternate between acute psychotic episodes and stable phases with full or partial remission.

During the acute phase of schizophrenia, which is a florid psychotic phase,treatment is aimed at alleviating or reducing acute symptoms, including violent and other dangerous behaviors, while improving role functioning. Frequently during this acute phase, patients exhibit hallucinations and/or delusions (positive symptoms), severely disorganized thinking, and usually are unable to care for themselves properly. Negative symptoms also often increase in severity during acute episodes.

It is during this acute phase that the combination of a valproate compound and an atypical antipsychotic has its greatest efficacy. The addition of a valproate compound will accelerate the rate at which the patient recovers from the acute phase of this disease. The psychotic symptoms associated with this phase of the disease will dissipate more quickly with the addition of a valproate compound to the treatment regimen.

The acute phase of schizophrenia has also been referred to as acute exacerbation of schizophrenia, acute psychosis associated with schizophrenia, and acute schizophrenia. For the purposes of this application, these terms should be treated as synonoms.

During the stabilization phase, which is characterized by decreasing severity of acute psychotic symptoms, therapy is aimed at minimizing stress and providing support to reduce the likelihood of relapse, enhance the patient's return to community life and facilitate continued reduction in symptoms and consolidation of remission. This phase can last for a period of 6 months, or longer, after the onset of an acute episode. During this phase of the illness, patients may also benefit from the combination of a valproate compound and an

atypical antipsychotic. Such a combination may reduce the incidence of the positive symptoms of schizophrenia and reduce the rate of relapse back to the acute state.

Once symptoms become relatively stabilized, the disorder enters the stable phase (also commonly referred to as the maintenance phase). Treatment during this phase is aimed at maintaining the patients level of functioning and quality of life, while preventing relapse. The combination of a valproate compound and an atypical antipsychotic may help prevent relapses back to the acute phase of schizophrenia. Other benefits for schizophrenics from the concurrent administration of a valproate compound and an atypical antipsychotic will become readily apparent to those skilled in the art.

Further information on the diagnosis and treatment of schizophrenia may be found in the Diagnostic and Statistical Manual of Mental Disorder, Revised, 4thEd. (2000), ("DSM- IV-TR"). The DSM- IV-TR was prepared by the Task Force on Nomenclature and Statistics of the American Psychiatric Association. Patients who would be considered schizophrenic according to the DSM criteria will typically benefit from the concurrent administration of an atypical antipsychotic and a valproate compound.

B) Atypical Antipsychotics

Atypical antipsychotics are well known to those skilled in the art. The essential feature of an atypical antipsychotic is that it has a high level of affinity for the $5HT_2$ receptor and functions as an antagonist of serotonin at that receptor. While the exact mechanism by which these compounds exert their antipsychotic effect is still under review, it is believed that at least part of their efficacy stems from their ability to modulate serotonergic transmission within the CNS. While atypical antipsychotics often have affinity for dopaminergic receptors within the CNS, they are much less potent dopaminergic antagonists than classical antipsychotics, such as chlorpromazine, haloperidol, etc. For a detailed discussion of these compounds and their mechanism of action, the readers attention is directed to Blin, Comparative Review of New Antipsychotics, Can J Psychiatry, Vol 44, 235-242 April 1999. In addition to their differing mechanism of action, atypical antispychotics can be differentiated from classical antipsychotics based upon their side effect profile. Atypical antipsychotics are associated with a significantly reduced incidence of acute extrapyramidal symptoms, especially dystonias, when compared to a typical antipsychotic such as haloperidol. (Beasley, et al., Neuropsychopharmacology, 14(2), 111-123, (1996)).

As used in this application, the term " atypical antipsychotic" includes, but is not limited to, olanzapine, clozapine, risperidone, sertindole, quetiapine, zotepine, eplivanserin, MDL 100 907, iloperidone, perospirone, blonanserin, Org-5222, SM-13496, aripiprazole and ziprasidone. Any other compound having a pharmacological profile analogous to the

compounds exemplified above should also be considered to be encompassed by the term atypical antipsychotic even if that compound discovered after the filing of this application.

Olanzapine, 2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno[2,3-b][1,5]benzodiazepine, is a known compound and is described in U.S. Pat. No. 5,229,382 as being useful for the treatment of schizophrenia, schizophreniform disorder, acute mania, mild anxiety states, and psychosis. U.S. Pat. No. 5,229,382 is herein incorporated by reference in its entirety. Olanzapine is available commercially from Eli Lilly. The recommend dose ranges from 2.5mg to 15 mg per day. A detailed discussion of olanzapine, its dosing schedule, potential side effects, etc., may be found in AHFS, Drug Information 2000, page 2135, which is published by the American Society of Hospital Pharmacists (editor-McEvoy).

Clozapine, 8-chloro-11-(4-methyl-1-piperazinyl)-5H-dibenzo[b,e][1,4]diazepine, is described in U.S. Pat. No. 3,539,573, which is herein incorporated by reference in its entirety. Clinical efficacy in the treatment of schizophrenia is described by Hanes et al, Psychopharmacol. Bull., 24, 62 (1988). Clozapine is available commercially from Novartis. Daily doses range from 25mg/day to 900mg/day. A detailed discussion of clozapine, its dosing schedule, potential side effects, etc., may be found in AHFS, Drug Information 2000, page 2125, which is published by the American Society of Hospital Pharmacists (editor-McEvoy).

Risperidone, 3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)piperidino]ethyl]-2-methyl-6,7,8,9-tetrahydro-4H-pyrido-[1,2-a]pyrimidin-4-one, and its use in the treatment of psychotic diseases are described in U.S. Pat. No. 4,804,663, which is herein incorporated by reference in its entirety. Risperidone is available commercially from Janssen. Daily doses range from 1mg per day to 16 mg per day. A detailed discussion of risperidone, its dosing schedule, potential side effects, etc., may be found in AHFS, Drug Information 2000, page 2142, which is published by the American Society of Hospital Pharmacists (editor-McEvoy).

Sertindole, 1-[2-[4-[5-chloro-1-(4-fluorophenyl)-1H-indol-3-yl]-1-piperidinyl]ethyl]imidazolidin-2-one, is described in U.S. Pat. No. 4,710,500. Its use in the treatment of schizophrenia is described in U.S. Pat. Nos. 5,112,838 and 5,238,945. U.S. Pat. Nos. 4,710,500; 5,112,838; and 5,238,945 are herein incorporated by reference in their entirety. Daily doses range up to 10mg per day.

Quetiapine, 5-[2-(4-dibenzo[b,f][1,4]thiazepin-11-yl -1-piperazinyl)ethoxy]ethanol, and its activity in assays which demonstrate utility in the treatment of schizophrenia are described in U.S. Pat. No. 4,879,288, which is herein incorporated by reference in its entirety. Quetiapine is typically administered as its (E)-2-butenedioate (2:1) salt. It is available commercially from Astra Zenecca. Daily doses range from 25mg per day to 750mg per day. A detailed discussion of quetiapine, its dosing schedule, potential side effects, etc., may be

found in AHFS, Drug Information 2000, page 2142, which is published by the Americal Society of Hospital Pharmacists (editor-McEvoy).

Ziprasidone, 5-[2-[4-(1,2-benzoisothiazol-3-yl)-1-piperazinyl]ethyl]-6-chloro-1,3-dihydro-2H-indol-2-one, is typically administered as the hydrochloride monohydrate. The compound is described in U.S. Pat. Nos. 4,831,031 and 5,312,925. Its activity in assays which demonstrate utility in the treatment of schizophrenia are described in U.S. Pat. No. 4,831,031. U.S. Pat. Nos. 4,831,031 and 5,312,925 are herein incorporated by reference in their entirety. Daily doses range from 5 mg day to 500mg/day.

Zotepine, 2-[(8-chlorodibenzo[b,f]thiepine-10-yl)oxy]-N,N-dimethylethylamine, is availiable commercially from Knoll under the tradename Zoleptil®. it is approved for use as a antipsychotic in Japan and Germany. Daily doses for adults range from 25mg/day to 300 mg/day.

Perospirone is marketed in Japan for schizophrenia by Yoshitomi. Daily doses range from 30mg to 300 mg daily. Further information regarding the compound can be obtained from Sumitomo Pharmaceutical, of Japan.

Bionanserin is under development as an antipsychotic in Japan by Dainippon Pharmaceuticals. It is currently reported to be in Phase III trials. Further information regarding the how to prepare the compound and relevant dosing information can be obtained from Dainippon. Aripiprazole is under development as an atipsychotic in Europe and the United Sates by Bristol-Myers Squibb. It is reported to be in phase III of human trials. Further information regarding how to prepare the compound and relevant dosage information can be obtain from Bristol-Myers Squibb.

SM-13496 is under development as an antipsychotic by Astra Zeneca and based on publicly available information is in Phase II clinical trials. Further information regarding how to prepare the compound and relevant dosing information can be obtained from Astra Zenecca.

Org-5222 is under development as an antipsychotic by Organon of the Netherlands and is reported to be in Phase II clinical trials. Further information regarding how to prepare the compound and relevant dosing information can be obtained from Organon.

MDL 100,907 is under development as an antipsychotic by Aventis. It is reported to be in Phase III trials. Further information regarding the compound can be found in United States Patent No. 6,063,793.

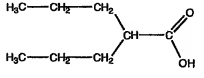
Iloperidone under development as an antipsychotic by Novartis and is reported to be in Phase III trials in Europe. Further information regarding the how to prepare the compound and relevant dosing information can be obtained from Novartis.

Eplivanserin was under development by Sanofi-Synthelabo as an antipsychotic. Further information regarding how to prepare the compound and relevant dosing information can be obtained from Sanofi.

C) Valproate Compounds

Several valproate compounds are currently available commercially in the United States or have been described in the literature.

One such compound is valproic acid. Valproic acid may be represented by the following structure:



Valproic acid is available commercially from Abbott Laboratories of Abbott Park, Illinois. Methods for its synthesis are described in Oberrelt, Ber. 29, 1998 (1896) and Keil, Z. Physiol. Chem. 282, 137 (1947). It's activity as an antiepileptic compound is described in the Physician Desk Reference, 52nd Edition, page 421 (1998). Upon oral ingestion within the gastrointestinal tract, the acid moiety disassociates to form a carboxylate moiety (I.e. a valproate ion).

The sodium salt of valproic acid is also known in the art as an anti-epileptic agent. It is also known as sodium valproate and is described in detail in The Merck Index, 12th Edition, page 1691 (1996). Further descriptions may be found in the Physician Desk Reference, 52nd Edition, page 417 (1998).

Divalproex sodium is effective as an antiepileptic agent and is also used for, migraine and bipolar disorder. Methods for its preparation may be found in United States Patent No.'s 4,988, 731 and 5,212,326, the contents of both which are hereby incorporated by reference. Like valproic acid, it also disassociates within the gastrointestinal tract to form a valproate ion. Divalproex sodium is available from Abbott Laboratories.

Dosages for divalproex sodium, valproic acid and sodium valproate are similar. They range from 250mg per day up to 1 gram per day, in selected patients up to 2 grams per day and on occasion up to 5 grams per day. A detailed discussion of these three compounds, their pharmacology, side effects, dosing schedule, etc. may be found in AHFS, Drug Information 2000, page 2142, which is published by the Americal Society of Hospital Pharmacists (editor-McEvoy).

In addition to these specific compounds, one of ordinary skill in the art would readily recognize that the carboxylic moiety of the valproate compound may be functionalized in a variety of ways. This includes forming compounds which readily metabolize *in-vivo* to produce valproate, such as valproate amide (valproimide), as well as other pharmaceutically acceptable amides and esters of the acid (i.e. prodrugs). This also includes forming a variety of pharmaceutically acceptable salts.

Suitable pharmaceutically acceptable basic addition salts include, but are not limited to cations based on alkali metals or alkaline earth metals such as lithium, sodium, potassium, calcium, magnesium and aluminum salts and the like and nontoxic quaternary ammonia and amine cations including ammonium, tetramethylammonium, tetraethylammonium, methylamine, dimethylamine, trimethylamine, triethylamine, diethylamine, ethylamine and the like. Other representative organic amines useful for the formation of base addition salts include ethylenediamine, ethanolamine, diethanolamine, piperidine, piperazine and the like.

Other possible compounds include pharmaceutically acceptable amides and esters. "Pharmaceutically acceptable ester" refers to those esters which retain, upon hydrolysis of the ester bond, the biological effectiveness and properties of the carboxylic acid and are not biologically or otherwise undesirable. For a description of pharmaceutically acceptable esters as prodrugs, see Bundgaard, E., ed., (1985) Design of Prodrugs, Elsevier Science Publishers, Amsterdam, which is hereby incorporated by reference. These esters are typically formed from the corresponding carboxylic acid and an alcohol. Generally, ester formation can be accomplished via conventional synthetic techniques. (See, e.g., March Advanced Organic Chemistry, 3rd Ed., John Wiley & Sons, New York p. 1157 (1985) and references cited therein, and Mark et al. Encyclopedia of Chemical Technology, John Wiley & Sons, New York (1980), both of which are hereby incorporated by reference. The alcohol component of the ester will generally comprise (i) a C_2 -C_{12} aliphatic alcohol that can or can not contain one or more double bonds and can or can not contain branched carbons or (ii) a C_7 -C_{12} aromatic or heteroaromatic alcohols. This invention also contemplates the use of those compositions which are both esters as described herein and at the same time are the pharmaceutically acceptable salts thereof.

"Pharmaceutically acceptable amide" refers to those amides which retain, upon hydrolysis of the amide bond, the biological effectiveness and properties of the carboxylic acid and are not biologically or otherwise undesirable. For a description of pharmaceutically acceptable amides as prodrugs, see Bundgaard, H., Ed., (1985) Design of Prodrugs, Elsevier Science Publishers, Amsterdam. These amides are typically formed from the corresponding carboxylic acid and an amine. Generally, amide formation can be accomplished via conventional synthetic techniques. (See, e.g., March Advanced Organic Chemistry, 3rd Ed.,

John Wiley & Sons, New York, p. 1152 (1985) and Mark et al. Encyclopedia of Chemical Technology, John Wiley & Sons, New York (1980), both of which are hereby incorporated by reference. This invention also contemplates the use of those compositions which are amides, as described herein, and at the same time are the pharmaceutically acceptable salts thereof.

As used in this application, any reference to "valproate" or " a valproate compound" should be construed as including a compound which disassociates within the gastrointestinal tract, or within in-vitro dissolution media, to produce a valproate ion including, but not limited to, valproic acid, the sodium salt of valproate, divalproex sodium, any of the various salts of valproic acid described above, and any of the prodrugs of valproic acid described above. Divalproex sodium is the most preferred valproate compound of the present invention.

D) Administration

As noted above, it has been discovered that schizophrenia can be treated by concurrently administering to a patient (i.e. a human) in need thereof, an atypical antipsychotic and a valproate compound. It has been discovered that this combination is especially useful during acute exacerbations of schizophrenia. The acute symptoms of schizophrenia will subside at a quicker rate in patients being treated with both a valproate compound and an atypical antipsychotic, when compared to treatment with only an atypical antipsychotic. The combination therapy is especially useful in relieving the positive symptoms of schizophrenia (i.e. hallucinations, delusions, paranoia, hostility, etc.)

As used in this application, the term "concurrent administration" refers to administering the valproate compound to a schizophrenic, who has been prescribed (or has consumed) at least one atypical antipsychotic, at an appropriate time so that the patients symptoms may subside. This may mean simultaneous administration of the valproate compound and the atypical antipsychotic, or administration of the medications at different, but appropriate times. Establishing such a proper dosing schedule will be readily apparent to one skilled in the art, such as a psychiatrist, or other physician.

The dosage range at which the atypical antipsychotic and the valproate compound will be administered concurrently can vary widely. The specific dosage will be chosen by the patients physician taking into account the particular antipsychotic chosen, the severity of the patients illness, any other medical conditions or diseases the patient is suffering from, other drugs the patient is taking and their potential to cause an interaction or adverse event, the patients previous response to these atypical antipsychotic, etc. As a general guideline however, the atypical antipsychotic and the valproate compound will be administered concurrently within the dosage guideline listed below:

a) olanzapine: from about 0.25 to 50 mg, once/day; preferred, from 1 to 30 mg, once/day; and most preferably 1 to 25 mg once/day;

b) clozapine: from about 12.5 to 900 mg daily; preferred, from about 150 to 450 mg daily;

c) risperidone: from about 0.25 to 16 mg daily; preferred from about 2-8 mg daily;

d) sertindole: from about 0.0001 to 1.0 mg/kg daily;

e) quetiapine: from about 1.0 to 40 mg/kg given once daily or in divided doses;

f) ziprasidone: from about 5 to 500 mg daily; preferred from about 50 to 100 mg daily;

g) zotepine; from about 25 mg to 500mg daily, more typically from about 75mg to 300 mg /day

h) divalproex sodium: from about 250mg to 5000 mg/day, preferably up to about 2500 mg per day

These guidelines reflect current dosage ranges for these medications, as generally accepted by the medical community. They are presented to further illustrate the invention and should not construed to limit it in any manner. The valproate compound and the atypical antipsychotic should be administered concurrently in amounts that are effective to treat the patient's schizophrenia. In more general terms, one would create a combination of the present invention by choosing a dosage of an atypical antipsychotic and a dosage of the valproate compound according to the spirit of the above guideline.

The antipsychotic therapy of the present invention is carried out by administering an atypical antipsychotic together with a valproate compound in any manner which provides effective levels of the compounds in the body at the same time. Valproate is absorbed from the GI tract via oral administration. All of the atypical antipsychotics exemplified above are absorbed from the GI tract. Typically, the combination will be administered orally.

However, the invention is not limited to oral administration. The invention should be construed to cover any route of administration that is appropriate for the medications involved and for the patient. For example, transdermal administration may be very desirable for patients who are forgetful or petulant about taking oral medicine. Injections may be appropriate for patients refusing their medication. One of the drugs may be administered by one route, such as oral, and the others may be administered by the transdermal, percutaneous, intravenous, intramuscular, intranasal or intrarectal route, in particular circumstances. The route of administration may be varied in any way, limited by the physical properties of the drugs and the convenience of the patient and the caregiver.

E) Formulations

The atypical antipsychotic and valproate compound may be administered as a single pharmaceutical composition, and so pharmaceutical compositions incorporating both compounds are important embodiments of the present invention. Such compositions may

take any physical form that is suitable for pharmaceuticals. Pharmaceutical compositions suitable for oral administration are particularly preferred. Such pharmaceutical compositions contain an effective amount of each of the compounds, which effective amount is related to the daily dose of the compounds to be administered. Each dosage unit may contain the daily doses of all compounds, or may contain a fraction of the daily doses, such as one-third of the doses. Alternatively, each dosage unit may contain the entire dose of one of the compounds, and a fraction of the dose of the other compounds. In such case, the patient would daily take one of the combination dosage units, and one or more units containing only the other compounds. The amounts of each drug to be contained in each dosage unit depends on the identity of the drugs chosen for the therapy, and other factors such as the indication for which the antipsychotic therapy is being given.

The inert ingredients and manner of formulating the pharmaceutical compositions are conventional, except for the presence of the combination of the present invention. The usual methods of formulation used in pharmaceutical science may be used here. All of the usual types of compositions may be used, including tablets, chewable tablets, capsules, solutions, parenteral solutions, intranasal sprays or powders, troches, suppositories, transdermal patches and suspensions. In general, compositions contain from about 0.5% to about 50% of the compounds in total, depending on the desired doses and the type of composition to be used. The amount of the compounds, however, is best defined as the effective amount, that is, the amount of each compound which provides the desired dose to the patient in need of such treatment. The activity of the antipsychotic combinations do not depend on the nature of the composition, so the compositions are chosen and formulated solely for convenience and economy. Any of the combinations may be formulated in any desired form of composition. Some discussion of different compositions will be provided, followed by some typical formulations.

Capsules are prepared by mixing the compounds with a suitable diluent and filling the proper amount of the mixture in capsules. The usual diluents include inert powdered substances such as starch of many different kinds, powdered cellulose, especially crystalline and microcrystalline cellulose, sugars such as fructose, mannitol and sucrose, grain flours and similar edible powders.

If desired, the capsules can be formulated so that the contents are removed from the capsules prior to ingestion by the patient. The medication may be diluted in foods, juices, etc., in order to simplify administration to those who have difficulty swallowing. For example, Abbott Laboratories sells a preparation known as Depakote Sprinke Capsules. Methods for manufacturing such a dosage form would be readily apparent to one skilled in the art.

The medications may also be formulated into liquids or syrups, as is known in the art, in order to simplify administration. The medication is dissolved in a liquid, flavorants, antioxidants, stabilizers etc. are added as is known in the art. Such dosage forms have particular suitability with the elderly, such as dementia patients.

Tablets are prepared by direct compression, by wet granulation, or by dry granulation. Their formulations usually incorporate diluents, binders, lubricants and disintegrators as well as the compound. Typical diluents include, for example, various types of starch, lactose, mannitol, kaolin, calcium phosphate or sulfate, inorganic salts such as sodium chloride and powdered sugar. Powdered cellulose derivatives are also useful. Typical tablet binders are substances such as starch, gelatin and sugars such as lactose, fructose, glucose and the like. Natural and synthetic gums are also convenient, including acacia, alginates, methylcellulose, polyvinylpyrrolidine and the like. Polyethylene glycol, ethylcellulose and waxes can also serve as binders.

A lubricant is necessary in a tablet formulation to prevent the tablet and punches from sticking in the die. The lubricant is chosen from such slippery solids as talc, magnesium and calcium stearate, stearic acid and hydrogenated vegetable oils.

Tablet disintegrators are substances which swell when wetted to break up the tablet and release the compound. They include starches, clays, celluloses, algins and gums. More particularly, corn and potato starches, methylcellulose, agar, bentonite, wood cellulose, powdered natural sponge, cation-exchange resins, alginic acid, guar gum, citrus pulp and carboxymethylcellulose, for example, may be used, as well as sodium lauryl sulfate.

Enteric formulations are often used to protect an active ingredient from the strongly acid contents of the stomach. Such formulations are created by coating a solid dosage form with a film of a polymer which is insoluble in acid environments, and soluble in basic environments. Exemplary films are cellulose acetate phthalate, polyvinyl acetate phthalate, hydroxypropyl methylcellulose phthalate and hydroxypropyl methylcellulose acetate succinate.

Tablets are often coated with sugar as a flavor and sealant. The compounds may also be formulated as chewable tablets, by using large amounts of pleasant-tasting substances such as mannitol in the formulation, as is now well-established practice. Instantly dissolving tablet-like formulations are also now frequently used to assure that the patient consumes the dosage form, and to avoid the difficulty in swallowing solid objects that bothers some patients.

When it is desired to administer the combination as a suppository, the usual bases may be used. Cocoa butter is a traditional suppository base, which may be modified by addition of waxes to raise its melting point slightly. Water-miscible suppository bases comprising, particularly, polyethylene glycols of various molecular weights are in wide use, also.

Transdermal patches have become popular recently. Typically they comprise a resinous composition in which the drugs will dissolve, or partially dissolve, which is held in contact with the skin by a film which protects the composition. Many patents have appeared in the field recently. Other, more complicated patch compositions are also in use, particularly those having a membrane pierced with innumerable pores through which the drugs are pumped by osmotic action.

F) Novel packaging

To enhance patient convenience, the atypical antipsychotic and the valproate compound may be formulated into a single dosage form. Alternatively, the atypical antipsychotic and the valproate compound may each be in separate dosage forms, but yet packaged in a single container for dispensing by the pharmacist (i.e. a blister pack). Such packaging is typically designed to help a patient comply with a dosage regimen and to consume all of the required medication.

Examples of such packaging are well known to those skilled in the pharmaceutical arts. For example, Pfizer distributes an antibiotic known as Zithromax®. Patients must consume 2 pills on the first day and one pill after that for 4 days in order to eradicate the infection. To allow a patient to comply with such a complicated schedule, Pfizer packages the medication in a blister pack that is commonly referred to as a Z-pack. Similar packages are used with steroids in which the dosage must be tapered. Birth control pills are another example of packaging pharmaceuticals to enhance convenience (i.e. articles of manufacture).

The atypical antipsychotic and the valproate compound may be incorporated into such packaging to enhance patient convenience. If desired, such packaging may be used even if the atypical antipsychotic and valproate compound are in a single dosage form. The particulars of such packaging will be readily apparent to one skilled in the art.

As is well known to those skilled in the art, the packaged pharmaceutical will include an insert which describes the drugs, their doses, possible side effects and indication. Thus, the invention should be construed to include a package containing at least one valproate compound in combination with an atypical psychotic. They may be in a single or separate dosage forms. The package will include an insert stating that the combination should be used to treat schizophrenia and move specifically acute exacerbations of schizophrenia.

G) Other Psychotic Disease

As noted above, the combination of an atypical antipsychotic and a valproate compound will have efficacy in psychoses associated with other mental illnesses besides schizophrenia. One such disease is schizophreniform disorder.

Schizophreniform is a condition exhibiting the same symptoms as schizophrenia, but is characterized by an acute onset with resolution in two weeks to six months. Often, schizophreniform is used to describe a patient's first schizophrenic episode. The patient presents with symptoms identical to those seen in the acute phase of schizophrenia, but the patient has no previous history of schizophrenia. Clinicians also refer to schizophreniform as "early schizophrenia".

The patients symptoms are similar to those exhibited during the acute phase of schizophrenia. (i.e. overtly psychotic behavior) which were described above in Section A. The combination of a valproate compound and an atypical antipsychotic will enhance the rate at which this psychotic behavior dissipates.

The discussion above in Sections B-F are equally relevant to treating schizophreniform disorder. The same atypical antipsychotics may be utilized in the same doses as described above. Likewise, the same valproate compounds may be utilized in the same doses as described above. The mode of administration, suitable formulations, packaging of products, etc. is the same as for schizophrenia.

Psychotic behavior may also be associated with dementia. Dementia is an organic mental disorder characterized a by a general loss of intellectual abilities involving impairment of memory, judgment, abstract thinking, as well as changes in personality. The most common causes of dementia are alzheimer's disease, parkinson's disease , and multi-infarct disease. If a patient with dementia exhibits psychotic behavior; the combination of a valproate compound and an atypical antipsychotic will enhance the rate at which this psychoses dissipates. As with schizophreniform, the discussion above in Sections B-F are equally relevant to any psychoses associated with dementia.

The following examples are being presented to further illustrate the invention. They should not be construed as limiting the invention in any manner.

H) Examples

The following typical formulae are provided for the interest and information of the pharmaceutical scientist.

Formulation 1

A hard gelatin capsule is prepared using the following ingredients:

	Quantity (mg/capsule)
Olanzapine	2.5

Divalproex sodium	500
Starch, dried	150
Magnesium stearate	10
Total mg	662.5

Formulation 2
A tablet is prepared using the ingredients below:

	Quantity (mg/capsule)
Olanzapine	1.25
Divalproex sodium	250
Cellulose, microcrystalline	275
Silicon dioxide, fumed	10
Stearic acid	5
Total mg	541.25

The components are blended and compressed to form tablets each weighing 541.25 mg.

Formulation 3
A tablet is prepared using the ingredients below:

	Quantity (mg/capsule)
Risperidone	1.0
Divalproex sodium	500
Cellulose, microcrystalline	275
Silicon dioxide, fumed	10
Stearic acid	5
Total mg	800

The components are blended and compressed to form tablets each weighing 791 mg.

Example 4

This study, which was randomized and double blinded was designed to examine the potential incremental benefit conferred by combining a valproate derivative, divalproex sodium, with a commonly used atypical antipsychotic agents (vs. antipsychotic monotherapy) in patients hospitalized for acute psychosis associated with schizophrenia.

There are three key assessments used to assess the efficacy of the combination treatment used in this trial: Positive and Negative Syndrome Scale (PANSS), (Kay et al., 1987) Brief Psychiatric Rating Scale – derived from the PANSS (BPRS-d), and the Clinical Global Impression (CGI) Scale (Guy, 1976). All of these assessments may be used to assess the clinical utility of antipsychotic agents. The PANSS is designed to measure severity of psychopathology in patients with schizophrenia. The PANSS Positive subscale

examines positive symptoms such as delusions and hallucinations; while the PANSS Negative subscale assesses negative symptoms of schizophrenia such as, emotional withdrawal and blunted affect. The BPRS is another standard assessment of psychopathology; it has items that overlap with those of the PANSS and therefore, can be derived from the PANSS as was done in the case with this study. The CGI is a two-part scale that assesses the clinician's impression of the patient's current state of illness (CGI -Severity) and the patient's improvement or worsening from baseline (CGI-Improvement).

PATIENTS AND METHODS

Patients

Patients between 18 and 65 years of age who were hospitalized with an acute exacerbation of schizophrenia were enrolled. Patients with a current DSM-IV diagnosis of schizophrenia, as confirmed by a Structured Clinical Interview for DSM-IV (SCID) conducted during screening (First et al. 1999), were selected for inclusion on the basis of having 1): a Positive and Negative Syndrome Scale (PANSS) Total score (Kay et al. 1987) of 60 or greater (based on a one- to seven-point scale) at the time of screening 2) scores on any two of the four items from the psychosis cluster of the BPRS, derived from the PANSS (BPRSd) (Kay et al. 1987) that corresponded to positive symptoms (i.e., hallucinatory behavior, unusual thought content, conceptual disorganization, and suspiciousness) totaling eight or greater 3) and, a total of six or greater on either hostility and uncooperativeness or excitement and tension. The eligible patient must have had a positive response to treatment with antipsychotics within the two years prior to enrollment in this study.

Patients were excluded from the study if they had a current diagnosis of schizoaffective disorder, drug-induced psychosis, manic episode, or depressive episode, as were those who had current serious violent, homicidal, or suicidal ideation. Also excluded from the study were pregnant or lactating females and patients with clinically significant abnormal laboratory data, unstable medical conditions, or an underlying condition that would confound the interpretation of study results.

Study Design

The study was a randomized, double-blind, parallel-group, multicenter trial, consisting of a wash-out period and a four-week double-blind treatment period. The protocol was approved by the institutional review board of each participating study site. Written informed consent was obtained from each patient or the patient's legally authorized representative before enrollment into the study.

After written informed consent was obtained, each patient who met entry criteria

entered the wash-out period of the study, which lasted for at least three times the mean elimination half-life of the antipsychotic or psychotropic medication that the patient was taking. Patients were then randomized to one of four treatment groups: 1) olanzapine monotherapy (Zyprexa®, Eli Lilly and Company); 2) risperidone monotherapy (Risperdal®, Janssen Pharmaceutical); 3) divalproex (Depakote® delayed release tablets, Abbott Laboratories) plus olanzapine; or 4) divalproex plus risperidone. The concurrent use of any antipsychotic medication other than the study drugs was not allowed during the study.

Divalproex was initiated on day 1 at 15 mg/kg/day (administered twice daily) and was titrated to clinical response, as deemed appropriate by the investigator, over 12 days to a maximum dosage of 30 mg/kg/day. Olanzapine and risperidone were initiated at 5 mg/day and 2 mg/day, respectively (administered once daily), increased to 10 mg/day and 4 mg/day, respectively, on day 3, and increased to a target daily dosage of 15 mg/day and 6 mg/day, respectively, on day 6. Once these dosages were achieved, they were to be continued for the remainder of the study. The investigators were instructed to discontinue the participation of any patient who could not tolerate the fixed target dosages of olanzapine or risperidone.

Certain adjunctive medications were allowed as needed during the wash-out and treatment periods, although not within eight hours prior to efficacy ratings. Chloral hydrate (up to 2 gm/day) or zolpidem tartrate (up to 10 mg/day) could be used for the control of insomnia. Lorazepam (up to 6 mg/day during the wash-out phase, up to 4 mg/day during Weeks 1 and 2 of the treatment period, and up to 2 mg/day during Week 3 of the treatment period) was permitted for control of severe agitation. The use of chloral hydrate, lorazepam, and zolpidem tartrate was prohibited during Week 4. Propranolol hydrochloride (per investigator's discretion) could be prescribed for akathisia, and benztropine mesylate (up to 4 mg/d) could be prescribed for control of extrapyramidal symptoms.

Patients were required to remain hospitalized for 28 days. However, leave from the hospital was allowed for up to 7 days, providing that the patient completed the two-week dosage titration phase and had a CGi-Improvement score of "much improved" after day 14. Patients on leave from the hospital were required to return to the study site for the regularly scheduled assessments, ratings, and procedures.

Clinical Evaluations

The protocol-defined psychiatric status of patients was evaluated using the PANSS Total and Subscales and the CGi Scale (Guy 1976). The evaluations were conducted on days 1 (baseline), 3, 5, 7, 10, 14, 21, and 28. The PANSS was scored as the patient had appeared over the previous 48 hours. The raters' proficiency had to meet pre-established criteria before the study commenced, and an interim assessment was conducted during the trial to assure the proficiency of the raters.

Safety Assessment

The data obtained to evaluate the safety of the study drugs included physical examinations, vital sign and body weight measurements, adverse events, and laboratory test results. Extrapyramidal side effects were assessed during the double-blind treatment period using a movement rating scale battery, including the Simpson-Angus Scale (SAS) (Simpson and Angus 1970), Barnes Akathisia Scale (BAS) (on days 1, 14 and 28) (Barnes 1989), as well as Abnormal Involuntary Movement Scale (AIMS) (days 1 and 28) (Guy 1976). Patients were monitored for adverse events between the time study drug was initiated and 30 days after the discontinuation of therapy, inclusive. Plasma concentrations of valproate were evaluated on day 28.

Statistical Analyses

The primary objective of this study was to evaluate the efficacy and safety of divalproex in the treatment of schizophrenia when combined with an atypical antipsychotic, with change from baseline to final evaluation on the PANSS Total Score being the primary efficacy endpoint.

All statistical tests were two-tailed, and p-values of 0.050, after rounding to three decimal places, were considered statistically significant. All analyses were performed with the SAS System (Version 6.12).

The two antipsychotic monotherapy groups were combined, as were the two combination therapy groups for comparisons of baseline characteristics and efficacy parameters. A target sample size of 120 patients each for the combined antipsychotic monotherapy group and the combined combination therapy group was selected in order to provide 80% power for an effect size of 0.362 and 90% power for an effect size of 0.418.

Efficacy analyses were performed on the intent-to-treat data set, which included all patients who received at least one dose of randomized study medication and had a PANSS Total score recorded at baseline and at least once during treatment. To address missing evaluations, a "last observation carried forward" analysis was conducted. This technique was used to reduce bias caused by patients who prematurely discontinued for lack of efficacy.

Baseline comparability between the combination and antipsychotic monotherapy groups for demographic characteristics was assessed by one-way analysis of variance (ANOVA) with treatment group as the main effect for quantitative variables (age, weight) and by Fisher's exact test for qualitative variables (gender, race). For statistical testing, race was categorized as Caucasian and non-Caucasian. For psychiatric history variables, baseline comparability between treatment groups was assessed by the Wilcoxon rank sum test (age at first diagnosis), by the Cochran-Mantel-Haenszel test (lifetime number of hospitalizations,

number of suicide attempts), and by Fisher's exact test (schizophrenia subtype). Baseline comparability among treatment groups for all efficacy and movement rating scale scores was assessed by two-way ANOVA with factors for treatment group and investigator. Treatment differences (combination therapy vs. antipsychotic monotherapy) in the percentage of patients prematurely discontinuing from the study were assessed by Fisher's exact test both for overall and for each individual item.

Comparisons of the combination and monotherapy groups were made for mean trough total valproic acid plasma concentrations using a mixed effects model (with effects for treatment group, visit, treatment group by visit interaction, study center, age, and weight).

Treatment differences in the percentage of patients who were granted hospital leave as well as the percentage of patients using adjunctive medication were assessed by Fisher's exact test. Treatment differences in the number and percentage of days each medication was prescribed and in the average daily dose of each medication were evaluated by a one-way ANOVA,

Treatment differences in the mean change from baseline to each evaluation for the PANSS Total score and subscales, BPRSd Total score and subscales, the supplemental anger item from the PANSS, and the CGI Severity score were assessed using a two-way ANOVA with factors for treatment and investigator. Because there were baseline differences for PANSS Positive Scale score and the PANSS individual item of delusions, an analysis of covariance (ANCOVA) with factors for treatment and investigator and with baseline as the covariate was conducted. A post-hoc repeated measures ANOVA was also conducted on observed cases data using PROC MIXED with fixed-effect factors for scheduled visit day, treatment, and investigator, and an AR (1) covariance structure. Treatment differences in the percentage of patients with at least a 20% and 30% improvement from baseline to final evaluation on the PANSS Total score at each scheduled visit were assessed by the Cochran-Mantel-Haenszel test, with investigators as strata.

For change from baseline to final value on PANSS Total score, an analysis of variance (ANOVA) was performed with factors for investigator, study drug (divalproex vs. placebo), type of antipsychotic (olanzapine vs. risperidone), and the interaction between study drug and antipsychotic. The test of interaction provided a test of the validity of combining treatment groups for the efficacy analyses.

Safety analyses were performed for all patients who received at least one dose of randomized study medication. Because of the differing safety profiles of olanzapine and risperidone, safety data for the each antipsychotic monotherapy group were compared with that of the corresponding divalproex/antipsychotic group. Fisher's exact test was used to assess treatment group differences in treatment-emergent adverse event incidence rates.

Treatment differences in mean change from baseline to final evaluation for the movement rating scales (SAS, BAS, AIMS) were assessed by a two-way ANOVA with factors for treatment and investigator. Treatment differences in laboratory data and vital signs (including weight) for mean change from baseline to the final evaluation were assessed by one-way ANOVA.

Results

Two hundred forty-nine patients were randomized at 29 investigative sites, and of these patients, 65 received olanzapine, 66 received divalproex and olanzapine, 60 received risperidone, and 58 received divalproex and risperidone. Of the 249 enrolled patients, 242 patients were included in the intent-to-treat analyses of efficacy, with four excluded because they did not have an on-treatment PANSS score and three excluded because they were randomized at two sites (only their second randomization was excluded from the efficacy analyses).

The treatment groups were similar at baseline based on demography, schizophrenia subtype, age at first diagnosis, number of past hospitalizations, and the number of suicide attempts (Table 1). The mean age of the intent-to-treat study population was 38.8 years (range, 18 to 63 years). The majority was male (76%), and there was an equal distribution between Caucasians (46%) and Blacks (49%). Most patients had a history of paranoid schizophrenia (82%), 56% were hospitalized six or more times for their schizophrenia, and 46% made at least one suicide attempt. At the time of their enrollment in the study, 214 patients (88%) were treated with an antipsychotic(s), including 78 patients (32%) with olanzapine and 81 patients (33%) with risperidone. The mean baseline PANSS score was 100 and 103 for patients in the antipsychotic monotherapy and combination therapy groups, respectively, with no significant difference between treatment groups.

A total of 83 (33%) patients prematurely discontinued their participation in the study; the most common reason being consent withdrawn (25 (20%) patients given antipsychotic monotherapy and 12 (10%) patients given combination therapy, $p \leq 0.05$). Seven patients (3 (2%) patients in the antipsychotic monotherapy group and 4 (3%) patients in the combination therapy group) discontinued their participation in the study because of treatment-emergent adverse events, as did 16 patients (6 (5%) and 10 (8%) patients in the respective treatment groups) for lack of efficacy. No statistically significant between-group differences were noted for overall premature discontinuation rates or premature discontinuation rates because of treatment-emergent adverse events or lack of efficacy.

The frequency with which patients left the hospital during the study was similar among the treatment groups. A third (32% in the monotherapy group and 35% in the combination

therapy group) had leave from the hospital during the study (mean hospital leave length of 4.2 and 4.9 days, respectively).

Dosing of Study Drugs and Adjunctive Medications

Most patients received the targeted therapeutic daily dosages of olanzapine (15 mg/day) and risperidone (6 mg/day) (Table 2). For olanzapine, 96% of patients in the monotherapy group and 95% of patients in the combination therapy group received the maximum dose by day 6. For risperidone, 94% of patients in the monotherapy group and 96% of patients in the combination therapy group received the maximum dose by day 6.

In the olanzapine and risperidone combination therapy groups, the mean modal daily dose of divalproex was 2364 mg (range, 500 - 3500 mg) and 2259 mg (range, 1000 - 3500 mg), respectively, resulting in final (day 28) mean trough total valproic acid plasma levels of 98.2 ± 31.4 µg/mL with olanzapine (n = 23 samples) and 100.2 ± 22.1 µg/mL with risperidone (n = 21 samples) (p = ns).

The use of adjunctive rescue medications (i.e., lorazepam, chloral hydrate, zolpidem, benztropine mesylate, and propranolol) during the study, including mg/day, number of days used, and percentage of patients using rescue medications, was similar among the treatment groups. Just over two-thirds (171/242) of the patients used at least one of these adjunctive medications during their participation in the study, including the use (at least one time) of lorazepam by 50% of patients (for a mean of 5.6 days) for agitation, propranolol by 8% of patients for akathisia, and benztropine mesylate by 19% of patients for extrapyramidal symptoms.

Efficacy Results

PANSS Total scores decreased (improved) throughout the 28-day treatment period in both the combination therapy and antipsychotic monotherapy groups (Figure 1).

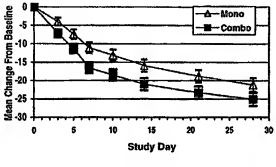


Figure 1: Mean Change From Baseline to Each Evaluation for PANSS Total Score

Statistically significant treatment differences in change from baseline PANSS Total score favoring combination therapy were observed as early as the third treatment day and persisted through day 21 ($p \leq 0.05$ at days 3,5, 14, and 21 and $p < 0.01$ at days 7 and 10). At day 28, the same trend ($p = 0.108$) was observed (mean change from baseline: -21.2, antipsychotic monotherapy and -25.1, combination). The change in effect size and variability over time are shown in Figure 2. Post-hoc repeated measures ANOVA of the change from baseline scores demonstrated a statistically significant treatment difference favoring combination therapy over antipsychotic monotherapy throughout the 28 days of the study for the PANSS Total score ($p = 0.020$).

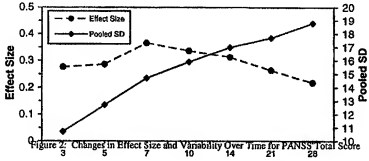


Figure 2: Changes in Effect Size and Variability Over Time for PANSS Total Score

In the ANOVA model (that included factors for investigator, study drug (divalproex vs. placebo), type of antipsychotic (olanzapine vs. risperidone), and the interaction between study drug and type of antipsychotic), the interaction term was not statistically significant, indicating that the effect of divalproex on PANSS Total scores was similar when added to either antipsychotic agent and supporting the validity of combining the two combination treatments and the two antipsychotic treatments for ANOVA analysis (Figure 3).

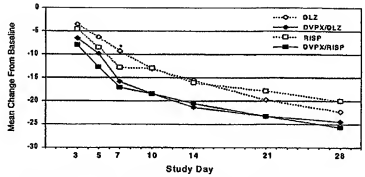


Figure 3: Mean Change From Baseline to Each Evaluation for PANSS Total Score for Each Treatment Group for Last Observation Carried Forward (Intent-to-Treat Dataset)

Clinical improvement, defined as a ≥ 20% or ≥ 30% reduction from baseline in PANSS Total score was consistently observed in a higher proportion of patients in the combination therapy group compared to the antipsychotic monotherapy group ($p \leq 0.05$ on days 3, 5, 7, and 10 for the ≥20% and ≥ 30% thresholds and on day 14 for ≥20% only) (Figure 4). A 20% or greater improvement in PANSS Total score was observed in 53% of patients in the combination group on day 7, but not until day 14 in the antipsychotic monotherapy group.

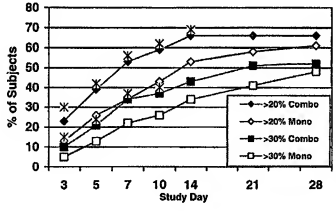


Figure 4: Percentage of Patients With ≥20% or ≥30% Improvement in PANSS Total Score

Improvements favoring combination therapy were also observed across all the evaluation points for mean PANSS Positive Scale score (Figure 5), with statistically significant treatment differences noted at days 3, 5, and 7 (by ANCOVA).

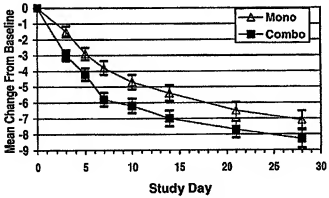


Figure 5: Mean Change From Baseline to Each Evaluation for PANSS Positive Scale Score

Improvements in mean PANSS General Psychopathology Scale score ($p < 0.05$ at days 5, 7, 10, and 14), and the PANSS Supplemental Anger Item ($p < 0.05$ at days 3 and 7) favoring combination therapy were also noted. PANSS Negative Scale showed little treatment difference ($p < 0.05$ at day 10). Post-hoc repeated measures ANOVA demonstrated a statistically significant treatment difference favoring combination therapy over antipsychotic monotherapy throughout the 28 days of the study for the PANSS Positive Scale score ($p = 0.002$) and the PANSS Supplemental Anger Item ($p = 0.02$), but not the PANSS Negative Scale score ($p = 0.167$). Furthermore, statistically significant treatment differences favoring the combination group over the antipsychotic monotherapy group were observed at four or more evaluation points for several PANSS individual items, including delusions (days 3, 7, 10, and 14 (ANCOVA), excitement (days 3, 7, 10, and 14), difficulty in abstract thinking (days 5, 7, 10, and 28), and unusual thought content (at all evaluation points).

Results of the BPRSd Total and subscales scores were consistent with those from the PANSS. Statistically significant treatment differences favoring the combination therapy group were noted at several evaluation points for BPRSd Total (days 3, 5, 7, 10, and 14), positive symptoms (days 3, 5, and 7), and agitation (days 7 and 14) scores. At day 28, a numerical, but not a statistically significant, difference was also noted. A post-hoc repeated measures ANOVA demonstrated a statistically significant difference favoring combination therapy over

antipsychotic monotherapy throughout the 28 days of the study for BPRSd Total ($p = 0.027$), Positive Symptoms ($p = 0.022$), and Agitation ($p = 0.023$) scores.

Statistically significant treatment differences were generally not observed for either CGI Severity or CGI Improvement scores. For both combination and antipsychotic monotherapy, mean CGI Severity scores decreased (improved) about one point from baseline at the end of the 28-day study, reflecting a change from "markedly mentally ill" to "moderately ill".

Safety Results

The use of combination therapy compared to monotherapy for schizophrenia showed both groups to be well tolerated. Discontinuations for adverse events were nearly the same and no adverse events were significantly greater with combination therapy. This is surprising since the addition of Depakote while keeping the same dose of the atypical antipsychotic might have been expected to produce difficulty with additional adverse events. There was more weight gain with Depakote added to olanzapine and risperidone (significantly more with risperidone) and reduction in platelets was more evident although not associated with any clinical events. Elevations of cholesterol were not observed on the combination but noted with both olanzapine and risperidone monotherapy. The addition of Depakote produced no clinically important safety issues other than greater weight gain when added to risperidone.

Discussion

In summary, the efficacy findings from this 4-week trial suggest that the combination of Depakote with the atypical antipsychotics, olanzapne or risperidone results in significantly greater improvement in the treatment of psychosis associated with schizophrenia compared to antipsychotic monotherapy. Significant treatment differences are observed as early as Day 3. Improvement is observed in the positive symptoms of psychosis as well as other symptoms that require acute management and stabilization in this patient population. Rapid stabilization of acute episodes of psychosis remains a challenging and under-investigated area in the treatment of schizophrenia. Improvement in time to stabilization impact patient safety, compliance and therapeutic outcomes. Taken together, the findings from this study have important implications for the treatment of acute psychosis in patients with schizophrenia.

List of Abbreviations and Definitions of Terms

AE	Adverse event
AIMS	Abnormal Involuntary Movement Scale
ALT	Alanine aminotransferase
ANOVA	Analysis of variance
APA	American Psychiatric Association
AST	Aspartate aminotransferase
BAS	Barnes Akathisia Scale
BPRS-d	Brief Psychiatric Rating Scale – derived (from the PANSS)
CGI	Clinical Global Impression Scale
CMH	Cochran-Mantel Haenszel
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
DSM-IV-TR	Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision
ECG	Electrocardiogram
EPS	Extrapyramidal Symptoms
GABA	Gamma-aminobutyric acid
GCP	Good Clinical Practice
ICH	International Conference on Harmonization
IRB	Institutional Review Board
LOCF	Last observation carried forward
PANSS	Positive and Negative Syndrome Scale;
SAE	Serious adverse event
SAS	Simpson-Angus Scale
SCID	Structured Clinical Interview for DSM-IV
VPA	Valproic Acid
WBC	White Blood Cell
YMRS	Young Mania Rating Scale

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Table 1. Baseline Demographic and Clinical Characteristics of Intent-to-Treat Patients

Characteristic	Antipsychotic Monotherapy (n=120)	Combination Therapy (n=122)
Gender, n (%)		
Female	29 (24%)	29 (24%)
Male	91 (76%)	93 (76%)
Race, n (%)		
Caucasian	54 (45%)	57 (47%)
Black	63 (53%)	56 (46%)
Other	3 (2%)	9 (7%)
Age (years)		
Mean ± S.D.	39.3 ± 10.5	38.3 ± 9.9
Range	18 – 60	19 - 63
Weight (lb)		
Mean ± SD	188.3 ± 40.8	190.1 ± 45.2
Range	120.2 – 306.0	111.0 – 329.0
Schizophrenia Subtype		
Paranoid	97 (81%)	101 (83%)
Disorganized	8 (7%)	4 (3%)
Undifferentiated	15 (13%)	17 (14%)
Age at First Diagnosis (years)		
Mean ± S.D.	25.0 ± 8.9	24.0 ± 7.8
Range	12 – 55	6 – 48
Lifetime Number of Hospitalizations		
Never	1 (<1%)	2 (2%)
1 – 5	55 (46%)	48 (39%)
6 – 10	28 (23%)	27 (22%)
> 10	36 (30%)	45 (37%)
Number of Suicide Attempts		
0	63 (53%)	69 (57%)
1 - 5	53 (44%)	48 (39%)
≥ 6	4 (3%)	5 (4%)
Mean PANSS Total score	100	103
Mean PANSS Positive Scale score	25.8	26.9
Mean PANSS Negative Scale score	25.2	26.0
Mean PANSS General Psychopathology Scale Score	49.1	50.1
Mean BPRSd Total Score	58.7	60.6
Mean CGI Severity	4.8	4.8

NOTE: $p > 0.05$ for all comparisons, except PANSS Positive Scale score ($p = 0.04$).

Table 2. Mean (± SD) Daily Dose of Antipsychotic Agent by Study Day and Treatment Group

	Olanzapine		Divalproex/ Olanzapine		Risperidone		Risperidone/ Divalproex	
Study Day	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)
1 - 2	*64*	*5.00 (0.00)*	*65*	*5.04 (0.31)*	*59*	*2.00 (0.00)*	*57*	*2.04 (0.26)*
3 - 5	*60*	*10.08 (057)*	*64*	*9.87 (0.95)*	*55*	*3.99 (0.20)*	*57*	*4.00 (0.18)*
≥6	*57*	*14.98 (0.13)*	*62*	*14.90 (0.65)*	*51*	*5.99 (0.03)*	*55*	*5.99 (0.03)*

We claim:

1. A method for the treatment of schizophrenia comprising concurrently administering to a patient in need thereof:
   a. a valproate compound, in an effective amount and;
   b. an atypical antipsychotic agent, in an effective amount.
2. The method according to claim 1 in which said valproate compound is divalproex sodium.
3. The method according to claim 1 in which said atypical antipsychotic agent is selected from the group consisting of olanzapine, risperidone, clozapine, quetiapine, ziprasidone, sertindole, zotepine, aripiprazole, eplivanserin, MDL 100, 907, iloperidone, perospirone, bionanserin, Org-5222, SM-13496 and ziprasidone.
4. The method according to claim 2 in which said antypsychotic agent is selected from the group consisting of risperidone and olanzapine.
5. A method for the treatment of acute psychosis associated with schizophrenia comprising concurrently administering to a patient in need thereof:
   a. a valproate compound, in an effective amount and;
   b. an atypical antipsychotic agent, in an effective amount.
6. The method according to claim 5 in which said valproate compound is divalproex sodium.
7. The method according to claim 5 in which said atypical antipsychotic agent is selected from the group consisting of olanzapine, risperidone, clozapine, quetiapine, ziprasidone, sertindole, zotepine, aripiprazole, eplivanserin, MDL 100, 907, iloperidone, perospirone, bionanserin, Org-5222, SM-13496 and ziprasidone.
8. A pharmaceutical composition comprising:
   a. at least one valproate compound, present in an effective amount;
   b. at least one atypical antipsychotic agent, present in an effective amount and;
   c. said valproate compound and said atypical antipsychotic agent are in admixture with at least one pharmaceutically acceptable excipient.
9. The pharmaceutical composition according to claim 8 in which said valproate compound is divalproex sodium.

10. The pharmaceutical composition according to claim 8 in which said atypical antipsychotic agent is selected from the group consisting of olanzapine, risperidone, clozapine, quetiapine, ziprasidone, sertindole, zotepine, aripiprazole, eplivanserin, MDL 100, 907, iloperidone, perospirone, blonanserin, Org-5222, SM-13496 and ziprasidone.

11. The pharmaceutical composition according to claim 9 in which said antipsychotic agent is selected from the group consisting of risperidone and olanzapine.

12. An article of manufacture comprising:

a. at least one pharmaceutical dosage form which contains a valproate, compound in an effective dose;

b. at least a second pharmaceutical dosage form which contains an atypical antipsychotic agent in an effective dose and;

c. said article contains said first and second dosage form, and

d. said article is suitable for distribution to a patient by a pharmacist.

13. The article of manufacture according to claim 12 in which said valprotate compound is divalproex sodium.

14. The article of manufacture according to claim13 in which said atypical antipsychotic agent is selected from the group consisting of risperidone and olanzapine.

15. The article of manufacture according to claim 13 in which container is a blister pak

16. A method for the treatment of schizophreniform disorder comprising concurrently administering to a patient in need thereof:

a. a valproate compound, in an effective amount and;

b. an atypical antipsychotic agent, in an effective amount.

17. A method for the treatment of acute psychosis associated dementia comprising concurrently administering to a patient in need thereof:

a. a valproate compound, in an effective amount and;

b. an atypical antipsychotic agent, in an effective amount

INTERNATIONAL SEARCH REPORT

PCT/US 03/02540

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/19 A61K31/55 A61K31/519 A61K31/496 A61K31/445

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

MEDLINE, BIOSIS, EPO-Internal, WPI Data, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	LAUTERBACH E C: "Catatonia-like events after valproic acid with risperidone and sertraline." NEUROPSYCHIATRY, NEUROPSYCHOLOGY, AND BEHAVIORAL NEUROLOGY. UNITED STATES JUL 1998, vol. 11, no. 3, July 1998 (1998-07), pages 157-163, XP008016703 ISSN: 0894-878X	1,3-5,7, 8,10-12, 14
Y	page 157, right-hand column, paragraph 1 ---	1-17
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Y	page 432, left-hand column, paragraph 3 ---	1-17

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

'A' document defining the general state of the art which is not considered to be of particular relevance

'E' earlier document but published on or after the international filing date

'L' document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

'O' document referring to an oral disclosure, use, exhibition or other means

'P' document published prior to the international filing date but later than the priority date claimed

'T' later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

'X' document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

'Y' document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

'&' document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
30 April 2003	17/06/2003

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Beranová, P

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	KANDO JUDITH C ET AL: "Concurrent use of clozapine and valproate in affective and psychotic disorders." JOURNAL OF CLINICAL PSYCHIATRY, vol. 55, no. 6, 1994, pages 255-257, XP008016701 ISSN: 0160-6689	1,3,5,7, 8,10,12
Y	page 257, left-hand column, paragraph 2 page 257, right-hand column, paragraph 2	1-17
X	NORRIE PETER D ET AL: "The use of Clozapine and sodium Valproate in schizophrenia: An open lot." NEUROPSYCHOPHARMACOLOGY, vol. 23, no. S2, August 2000 (2000-08), page S135 XP008016704 Second International Congress on Hormones, Brain and Neuropsychopharmacology;Rhodes, Greece; July 15-19, 2000 ISSN: 0893-133X	1,3,5,7, 8,10,12
Y	Abstract	1-17
X	WO 00 72837 A (SEPRACOR INC) 7 December 2000 (2000-12-07)	1,3,5,7, 8,10,12
Y	page 10, line 9	1-17
X	WO 00 59489 A (SEPRACOR INC) 12 October 2000 (2000-10-12)	1,3,5,7, 8,10,12
Y	claims 3,7,16,18,20	1-17
X	WO 97 35584 A (LILLY CO ELI) 2 October 1997 (1997-10-02) claims 1,2	8,10-12, 14
X	WO 97 35586 A (LILLY CO ELI) 2 October 1997 (1997-10-02) claims 1,15	8,10-12, 14
Y	ROTHSCHILD ANTHONY J ET AL: "Olanzapine response in psychotic depression." JOURNAL OF CLINICAL PSYCHIATRY, vol. 60, no. 2, February 1999 (1999-02), pages 116-118, XP008016700 ISSN: 0160-6689 page 117, right-hand column, paragraph 2	1-17

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
Y	SPINA EDOARDO ET AL: "Plasma concentrations of risperidone and 9-hydroxyrisperidone: Effect of comedication with carbamazepine or valproate." THERAPEUTIC DRUG MONITORING, vol. 22, no. 4, August 2000 (2000-08), pages 481-485, XP008016699 ISSN: 0163-4356 page 484, left-hand column, paragraph 1 page 484, right-hand column, paragraph 2	1-17
A	BALDESSARINI ROSS J ET AL: "Hospital Use of Antipsychotic Agents in 1989 and 1993: Stable Dosing With Decreased Length of Stay." AMERICAN JOURNAL OF PSYCHIATRY, vol. 152, no. 7, 1995, pages 1038-1044, XP008016702 ISSN: 0002-953X Entire document	
A	SANDERS R D ET AL: "Edema associated with addition of risperidone to valproate treatment." THE JOURNAL OF CLINICAL PSYCHIATRY. UNITED STATES DEC 1998, vol. 59, no. 12, December 1998 (1998-12), pages 689-690, XP008016705 ISSN: 0160-6689 Entire document	

INTERNATIONAL SEARCH REPORT

PCT/US 03/02540

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 1 - 7, 16 and 17 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [X] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Present claims 1, 2, 5, 7, 8, 9, 12, 13, 16 and 17 relate to a compound defined by reference to a desirable characteristic or property, namely "atypical antipsychotic agent". The claims cover all compounds having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and disclosure within the meaning of Article 5 PCT for only a very limited number of such compounds. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the compound by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible. Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to olanzapine, risperidone, clozapine, quetiapine, ziprasidone, sertindole, zotepine, aripiprazole, aplivanserin, MDL 100, 907, iloperidone, perospirone, blonanserin, Org-5222, SM-13496 and ziprasidone.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

PCT/US 03/02540

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